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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,199	07/11/2001	Jack R. Wands	21486-032DIV4	1568

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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/903,199	WANDS ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *26 and 41-47* is/are pending in the application.

4a) Of the above claim(s) *41 and 43-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *26, 42, 46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claim 26 has been amended. Claims 27, 39 and 40 have been canceled. Claims 46 and 47 have been added. Claims 26 and 41-47 are pending. Claims 41, 43-45 remain withdrawn from consideration. Claims 26, 42, 46 and 47 are under consideration.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

3. Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 46 recites the limitation "said mutation" which lacks antecedent basis in claim 26.

4. Claim 47 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. New claim 47 is broadly drawn to a method of inhibiting hydroxylation of an aspartic acid or asparagine residue of an EGF-like repeat sequence comprising the amino acid sequence of SEQ ID NO:4. The response (page 6, lines 6-8) indicates that new claim 47[27] is supported by the disclosure at page 9, lines 18-29, page 13, lines 1-9 and page 5, lines 18-19. This has been considered but not found persuasive. The cited text refers only to NOTCH polypeptides. This does not support a broader claim to any protein comprising SEQ ID NO:4. Additionally, it is recognized in the art that TGF-beta, FBL, FBRL, NIDO PRTS and S1-5, all comprise SEQ ID NO:4 (Lecka-Czernik et al, Molecular and Cellular Biology, 1995, Vol. 15, pp. 120-128, Figure 5, reference C20 of the IDS filed November 21, 2001). The specification as filed does not contemplate other proteins outside of NOTCH in a method comprising the inhibition of hydroxylation . Thus, claim 47 represents new matter.

5. Claims 26, 42, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lavaissiere et al (Journal of Clinical Investigation, 1996, Vol. 98, pp. 1313-1323, cited in the previous Office action) as evidenced by Kelley et al (Cell, Vol. 51, pp. 539-548, reference C14 of the IDS filed November 21, 2001) and Lecka-Czernik et al (Molecular and Cellular Biology, 1995, Vol. 15, pp. 120-128, reference C20 of the IDS filed November 21, 2001) in view of Jia et al (PNAS, 1994, Vol. 91, pp. 7227-7231, cited in the previous Office action).

Claim 26 is drawn to a method for inhibiting tumor growth in a mammal comprising administering to a liver cell in said mammal a compound which inhibits hydroxylation of an aspartic acid or an asparagine residues of a EGF-like repeat sequence of a NOTCH polypeptide by an endogenous human aspartly (asperaginyl) beta-hydroxylase (HAAH) polypeptide, wherein said repeat sequence comprising the amino acid sequence of SEQ ID NO:4, and wherein said cell overexpresses said HAAH polypeptide and wherein said HAAH polypeptide comprises the amino acid sequence of SEQ ID NO:2. Claim 42 embodies the method of claim 26 wherein said tumor is a hepatocellular carcinoma. Claim 46 embodies the method of claim 26 wherein said mutation is a substitution which changes a ferrous ion binding site from histidine to a non-iron binding amino acid. It is noted that the metes and bounds of claim 46 cannot be determined for the reason set forth in the rejection under 112, second paragraph above, however it is included in the instant rejection because the ferrous ion binding site in aspartly (asperaginyl) beta-hydroxylase is recognized in the art.

Claim 47 is drawn to a method of inhibiting tumor growth in a mammal comprising administering to said mammal a polypeptide comprising a mutation at position 671, 675, 679 or 690 of SEQ ID NO:2, wherein said polypeptide inhibits hydroxylation of an aspartic acid or asparagine residue by an EGF-like repeat sequence comprising the amino acid sequence of SEQ ID NO:4 by an endogenous HAAH polypeptide in a cell that overexpresses said HAAH polypeptide, wherein the HAAH polypeptide comprises the amino acid sequence of SEQ ID NO:2.

Lavaissiere et al teach that the monoclonal antibody, FB-50, binds to an epitope of HAAH, and that this epitope is present in hepatocellular carcinoma tissues (page 1315, Table1, and page 1316, second column, lines 10-12). Lavaissiere et al teach that hydroxylase activities in liver carcinoma cells were substantially higher than hydroxylase activities in adjacent non-

cancerous tissue (page 1321, first column, first full paragraph). Lavaissiere et al correlate the increase in hydroxylation with and increase in HAAH expression (abstract, lines 21-30). The aspartly (asperaginyl) hydroxylase of Lavaissiere et al is the human enzyme and this would inherently comprise the amino acid sequence of SEQ ID NO:2. Lavaissiere et al teach the His-motif (amino acid residues 679-697) contains a histidine residue essential for binding iron and said His-motif is identical to the His motif found in the bovine aspartyl (asperaginyl) hydroxylase (page 1320, first column, lines 9-10). Lavaissiere et al suggest that the NOTCH signal transduction pathway is regulated by NOTCH hydroxylation which can regulate ligand binding and effect the activity of NOTCH cytoplasmic domain known to be oncogenic (page 1313, second column, lines 29-34, under the heading of "Introduction"). Lavaissiere et al do not teach a method of inhibiting tumor growth in a mammal comprising the administration of a compound which inhibits the hydroxylation of a NOTCH polypeptide by HAAH.

Kelley et al identify the consensus sequence for the EGF repeat in NOTCH which is the same as SEQ ID NO:4 (page 543, legend of figure 2, part B, "derived consensus").

Lecka-Czernik et al identify the aspartyl residue which is hydroxylated in NOTCH (page 125, figure 5, last line of legend).

Jia et al teach that alanine substituted in place of histidine at residue 675 of bovine aspartyl (asperaginyl) hydroxylase results in loss of iron binding and loss of hydroxylase activity (page 7231, first column, lines 3-4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer to the liver of a mammal having hepatocellular carcinoma, a mutant of the HAAH polypeptide, wherein said mutation comprises a substitution of alanine for histidine at residue 675. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Lavaissiere et al correlating the increase in hydroxylation of NOTCH to the increase in the activity of the cytoplasmic domain of NOTCH which is known to be oncogenic, and the further teachings of Lavaissiere et al identifying histidine in the His motif of HAAH which is necessary for the hydroxylation activity of HAAH and teaching that said His motif is identical to the His motif found in bovine , aspartyl (asperaginyl) hydroxylase; and the teachings of Jia et al demonstrating that mutation of the histidine residue at position 675 in bovine aspartyl (asperaginyl) hydroxylase

results in loss of the hydroxylation activity of the enzyme. One of skill in the art would be motivated to decrease the hydroxylation of NOTCH in order to decrease the oncogenic activity of the cytoplasmic domain of NOTCH, and one of skill in the art would recognize that mutant HAAH polypeptide incapable of hydroxylating NOTCH would antagonize the hydroxylation activity of the wild-type HAAH polypeptide.

6. All other rejections and objections as set forth in Paper No. 11 are withdrawn in light of applicants amendments.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

9/23/03

Karen A. Canella